REMARKS

Regarding the Prosecution History:

Applicants are thankful for the examiner's efforts to clarify the incomplete non-final Office action mailed April 16, 2007 by issuing the Office communication mailed June 04, 2007, wherein the examiner stated that "the incomplete sentence that appears on page 9, would have merely re-stated the examiner's reasoning on page 6...." Now that the incomplete non-final Office action mailed April 16, 2007 has been clarified, applicants are able to provide a reply to the non-final Office action mailed April 16, 2007. Upon careful review of the remarks presented in this reply, the examiner will agree that the claimed invention is patentable and that this application is in good condition for allowance.

In the incomplete non-final Office action mailed April 16, 2007, as completed by the Office communication mailed June 04, 2007, the examiner rejected:

I. Claims 2 – 10 under 35 U.S.C. §103(a) over Baert et al. (US 6,365,188) in view of Stella et al. (US 6,046,177) in further view of Oshlack et al. (US 6,306,438) or Murata et al. (US 5,500,221);
II. Claims 2 – 10 under 35 U.S.C. §103(a) over Tsuboi et al. (US 6,063,393); or over Tsuboi et al. in view of Klimesch et al. (US 4,880,585).

Regarding the Claim Amendments presented in this reply:

The amendments to the claims add no new matter. Support for the inclusion of alkyl celluloses and hydroxyalkyl celluloses into the list of polymeric binders finds support on page 4, line 17 of the specification. The limitation that the active ingredient and cyclodextrin are molecularly dispersed in the polymeric binder so that a solid solution is produced finds support at page 15, line 43 to page 16, line 3 of the specification.

Regarding Rejection I:

Baert et al. relates to a "[p]rocess for preparing a solid mixture comprising one or more cyclodextrins and an insoluble active ingredient characterized in that said process comprises a melt-extrusion step, wherein the active ingredient is embedded into the cyclodextrin carrier."[1] The "melt-extrusion step comprises the following substeps: a) mixing one or more cyclodextrins with the active ingredient or active ingredients, b) optionally mixing additives, c) heating the thus obtained mixture until melting of one of the components, d) forcing the thus obtained mixture through one or more nozzles; e) cooling the mixture till [*sic*] it solidifies."[2] The examiner has erred by suggesting that "one would have been motivated to add a polymer such as instant polymer in the instant amount, to modify the release rate of the dosage form."[3] According to the Stella et al. reference, "the term 'release rate modifier' refers to a substance which will modify the rate of release of the therapeutic agent from the pharmaceutical formulation according to the invention."[4] The reference also points out that "It will be understood that some of the binders mentioned herein can also be considered release rate modifiers."[5] However, the Stella et al. reference provides no guidance as to which binders can be considered release rate modifiers. The examiner's selection, therefore, is clearly based on an impermissible form of hindsight reasoning, whereby the examiner has taken into account knowledge which was not within the level of ordinary skill in the art at the time the claimed invention was made, but instead includes "knowledge gleaned only from applicant's disclosure."[6]

In KSR International Co. v. Teleflex Inc., 127 S. Ct. 1727 (2007), the United States Supreme Court stated that the Graham v. John Deere Co. of Kansas City, 383 U.S. 1 (1966), factors still control an obvious inquiry, and made clear that in order to establish a *prima facie* case of obvious "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention

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[1] Abstract US 6,365,188.
[2] Column 4, indicated lines 14 – 23 of US 6,365,188.
[3] Page 6, lines 14 – 16 of the incomplete Office action mailed 04/16/2007.
[4] Column 27, indicated lines 41 – 44 of US 6,046,177.
[5] Column 27, indicated lines 49 – 51 of US 6,046,177.
[6] MPEP 2145, citing *In re McLaughlin* 443 F.2d 1392, 1395, 170 USPQ 209, 212 (CCPA 1971).

does"[7] must be identified. "Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound."[8] As discussed above, the examiner has taken into account knowledge which was not within the level of ordinary skill in the art at the time the claimed invention was made, but instead includes "knowledge gleaned only from applicant's disclosure."[9] The examiner has failed to identify a reason in the prior art that would have led a skilled artisan to make the proposed selection from within the Stella et al. reference and subsequently to make the proposed modification to the Baert et al. reference.

Example 10 is the only example in Stella et al. that is directed to melt extrusion. In this example, the amount of polymeric components (PEG 6000 + HPMC K15M) is only 23% by weight of the overall granulation. This is less than half the amount required by the present claims, which require at least 50% by weight of at least one polymeric binder. Moreover, the reference does not teach or suggest that the amount of these polymeric binders is determinative of the release properties. Example 10 merely states that "[t]hese tablets containing drug in the form of a physical blend will hydrate in a dissolution medium or in the gastrointestinal tract to slowly release the diltiazem by diffusion and erosion mechanisms."[10] In other words, the weight percentage of the polymeric components in example 10 of Stella et al. were not identified as result effective parameters, and the modifications that would have been needed to arrive at the present invention cannot, as a matter of law, be classified as "optimization achievable via routine experimentation."

Finally, claim 8 as amended requires that the active ingredient and the cyclodextrin are molecularly dispersed in the polymeric binder so that a solid solution is produced. The cited references fail to teach or suggest this feature. To help make clear that the cited references fail to teach or suggest this feature, reference is made to Drug Development and Industrial Pharmacy, Vol. 29, No. 6, pp. 641 – 652, 2003. On page

[7] KSR International Co. v. Teleflex Inc., 127 S. Ct. 1727 at 1731 (2007).
[8] Takeda Chemical Industries, Ltd. et al. v. Alphapharm Pty. Ltd et al., Case Number: 06-1329, *8 (Fed. Cir., June, 28, 2007).
[9] MPEP 2145, citing *In re McLaughlin* 443 F.2d 1392, 1395, 170 USPQ 209, 212 (CCPA 1971).
[10] Column 45, indicated lines 27 – 30 of US 6,046,177.

645 of Drug Development and Industrial Pharmacy it is explained that:

> When all the itraconazole has dissolved in the components upon melting, a solution will be formed, which upon cooling may form a solid solution; the solid solution will have a clear aspect. ... Presumably a high fraction of HPMC is necessary for dissolving all the itraconazole in the mixture.

Further, page 649, left column to right column of Drug Development and Industrial Pharmacy state that:

> The effect of melt-extrusion on the apparent itraconazole solubility in 0.1 N HCL was significant; the apparent itraconazole solubility in 0.1 N HCL of the extruded mixture was approximately 5 to 30 times higher than that of the physical mixtures. The effect was more pronounced for the clear extrudates ... compared to the turbid extrudates.

Further, page 650, left column of Drug Development and Industrial Pharmacy states that:

> For optimization of a formulation with an itraconazole fraction of 40% w/w, the following rules were applied: clear extrudates must be obtained, ... the visual aspect results indicated that HPMC fraction must be high (>33% w/w) to obtain clear extrudates.

Thus, it follows that "solid solutions" (as evidenced by the discussion regarding "clear extrudates") are preferred due to their enhanced solubility. The behavior of solid solutions is distinct from physical mixtures of equal composition. The solid solutions are obtained by melt-extrusion. The amount of polymeric binder (PEG 6000 + HPMC K15M) utilized in example 10 of Stella et al. is 23%. This figure is considerably below the value of 33% that is necessary to obtain clear extrudates, as evidenced above. Thus, it should be clear that the cited references fail to teach or suggest the limitation of claim 8 as amended that the active ingredient and the cyclodextrin are molecularly dispersed in the polymeric binder so that a solid solution is produced.

Regarding Rejection II:

Tsuboi "relates to a process for the treatment of individual plants with solid shaped plant treatment agents which are introduced into the sap conduction paths of the plants" (page 2, lines 1 – 2) not to solid dosage forms suitable for oral and rectal administration for humans and animals. Also, Tsuboi et al. do not disclose the polymeric binders required by the amended claims. Tsuboi et al. only disclose use of Biopol and Carbowax 20M. The examiner admits that "Tsuboi does not specify the use of polyvinylpyrolidone [PVP]."[11] However, the examiner argues that Klimesch et al. teach that PVP was "conventionally used in the preparation of pharmaceutical tablets[,]"[12] and that, therefore, a skilled artisan would have utilized it in Tsuboi et al.'s method.

However, the examiner has not established a *prima facie* case of obviousness. "It [is] necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound."[13] The mere allegation that Klimesch et al. teach that PVP was "conventionally used in the preparation of pharmaceutical tablets[,]"[14] is insufficient. Moreover, the examiner's mere allegation that a skilled artisan would have had a reasonable expectation of success upon making the proposed combination is insufficient to support a *prima facie* case of obviousness absent a citation to some technical details in the prior art references. Absent objective evidence or an Examiner's affidavit that this information was know by a person of ordinary skill in the art at the time the invention was made, the comments in the Office Action are mere speculation and impermissible to use in establishing *prima facie* obviousness. If however, contrary to Applicant's assertions above, the Examiner has personal information not of record used to determine "sufficient" numbers of examples, Applicant respectfully requests an Examiner's affidavit, as set forth in MPEP 1.104(c)(D)(2), indicating the use of personal knowledge and allowance for Applicant to respond to said personal knowledge

[11] Page 10, line 21 of the present Office action.
[12] Page 11, lines 3 – 4 of the present Office action.
[13] Takeda Chemical Industries, Ltd. et al. v. Alphapharm Pty. Ltd et al., Case Number: 06-1329, *8 (Fed. Cir., June, 28, 2007).
[14] Page 11, lines 3 – 4 of the present Office action.

In Conclusion:

The present application is in condition for allowance. Again, applicants are thankful for the examiner's diligent efforts to advance this application to allowance, and request favorable action in this matter.